REMARKS

The Amendment

Applicants amend Claim 25 in the interest of expediting prosecution of the present application. Applicants reserve the right to file the original claims in one or more continuation type applications.

The abstract is amended to mention the invention to which the claims are directed. Support for this amendment is found, for example, in page 3, lines 11-13.

Claim 25 is amended to recite "consisting" instead of "comprising". Support for this amendment is found, for example, in Example 2 (page 31, line 32 to page 32, line 29).

No new matter is added to any of the above amendment. The Examiner is requested to enter the amendments.

Remarks

Claims 25 and 34-42 are rejected in the present application.

1. Rejection under 35 U.S.C. § 112, second paragraph.

The Examiner rejects Claim 42 under 35 U.S.C. 112, second paragraph as allegedly being indefinite for the term "PASI". Applicants traverse this rejection.

The specification teaches that "PASI" is the "Psoriasis Area Severity Index" by which the severity of psoriasis is measured (Page 17, lines 1-3). The specification cites Fleischer, *et al.* (*J. Dermatol.* 26:210-5, 1999; a copy of the abstract is attached). Fleischer, *et al.* shows that PASI is a well known means for measuring the severity of psoriasis for one of ordinary skill in the art. Applicants also bring to the Examiner's attention the disclosure of Gebhardt, *et al.* (*Allergy* 52:1087-94, 1997; a copy of the abstract is attached). Gebhardt, *et al.* shows that PASI is a well known means for measuring the severity of psoriasis for one of ordinary skill in the art at the time the present application was filed. Therefore, the term "PASI" is clear and definite.

According, Applicants respectfully request the Examiner to withdraw this rejection.

2. Rejections under 35 U.S.C. § 102(a)

The Examiner rejects Claims 25, 34-37, and 39-42 as allegedly being anticipated by Strober, *et al.* (WO 98/16248, IDS). In the interest of expediting prosecution, Applicants avoid this rejection by amending Claim 25.

The Examiner asserts that: "Strober et al. teach a method of enhancing oral tolerance to treat an autoimmune disease by administering a monoclonal antibody that binds IL-12 and inhibits its effect, along with an orally administered antigen" (page 4, lines 17-18). Strober, *et al.* disclose a method of treatment that requires the administration of two compounds, an antigen associated with the autoimmune disease and an inhibitor of IL-12 (page 3, lines 14-18). The example provided by Strober, *et al.* involves a treatment that requires two compounds: the feeding of OVA and the injection of anti-IL-12 antibody. Amended Claim 25 is directed to a method of treating a patient suffering from psoriasis consisting the step of administering to the patient a pharmaceutical formulation comprising an antibody that binds to interleukin 12. Since Strober, *et al.* do not teach any method consisting the step of administering to a patient a pharmaceutical formulation comprising an antibody that binds to interleukin 12, Strober, *et al.* do not anticipate Claim 25, or Claims 34-37 and 39-42 which depend from Claim 25..

According, Applicants respectfully request the Examiner to withdraw this rejection.

3. Rejection under 35 U.S.C. § 102(b)

The Examiner rejects Claims 36-37, and 40-42 as allegedly being anticipated by Strober, *et al.* (WO 98/16248).

For the reasons stated earlier, Strober, *et al.* do not anticipate Claims 36-37, and 40-42. Strober, *et al.* disclose a method of treatment that requires the administration of two compounds, an antigen associated with the autoimmune disease and an inhibitor of IL-12 (page 3, lines 14-18). Claims 36-37, and 40-42 depend from Claim 25, which is directed to a method of treating a patient suffering from psoriasis consisting the step of administering to the patient a pharmaceutical formulation comprising an antibody that

binds to interleukin 12.

According, Applicants respectfully request the Examiner to withdraw this rejection.

4. Rejections under 35 U.S.C. § 103(a)

The Examiner rejects Claims 25, 34-37, and 39-42 as allegedly being unpatentable over Gillies, *et al.* (WO 96/40093) in view of Leonard, *et al.* (U.S. Patent No. 6,338,848).

Gillies, *et al.* disclose the use of certain bis-phenol or -phenoxy compounds in the stimulation of the immune system to inhibit the IL-12 induced production of interferon-γ (IFN-γ) in order to modulate induction of Th2 cells (page 3, lines 22-26). Gillies, *et al.* further disclose that the "bis-compounds may be used topically for the treatment of skin diseases, such as psoriasis" (page 25, lines 14-15).

Leonard, *et al.* disclose methods of treating autoimmune diseases by administering antagonists of IL-12 to inhibit IFN-γ production. Leonard, *et al.* further disclose that:

> "Administration can be carried out in a variety of convention ways. Intraperitoneal injection is the preferred method of administration of the IL-12 antagonist or IL-12. Intravenous, cutaneous or sub-cutaneous injection may also be employed." (col. 7, lines 1-5).

There is no suggestion or motivation to combine the disclosure of Leonard, *et al.* with Gillies, *et al.*

This is because the method for treating psoriasis disclosed by Gillies, *et al.* is limited to topical administration of the bis-compounds, while Leonard, *et al.* disclose the administration of anti-IL-12 antibody by injection. Gillies, *et al.* do not teach or suggest treating psoriasis using any other form of administration, while Leonard, *et al.* disclose administering anti-IL-12 antibodies in general (col. 2, lines 42-45) but do not teach or suggest administering them topically. Leonard, *et al.* only disclose the specific administrations by injection (col. 7, lines 1-5). There is no suggestion or motivation to combine a method of treatment of psoriasis by topical administration with any method that administers by injection. Therefore, the disclosures of Leonard, *et al.* and Gillies, *et al.* should not be combined.

There is no reasonable expectation of success that administering the anti-IL-12 antibody of Leonard, *et al.* would be successful in treating a patient suffering from psoriasis using the method of Gillies, *et al.*

There is no reasonable expectation of success because the method for treating psoriasis disclosed by Gillies, *et al.* is limited to topical administration of the bis-compounds, while Leonard, *et al.* discloses administering the anti-IL-12 antibodies by injection. There is no suggestion or motivation that administering the anti-IL-12 antibodies of Leonard, *et al.* using the topical administration method of Gillies, *et al.* would be successful in treating psoriasis. A method of treating psoriasis by topical administration of small molecule bis-compounds does not suggest or motivate that one of ordinary skill in the art should reasonably expect that replacing the small molecule bis-compounds with anti-IL-12 antibodies in the method of Gillies, *et al.* would be successful in treating psoriasis.

Further, there is no reasonable expectation of success because the method for treating psoriasis disclosed by Gillies, *et al.* uses small molecule bis-compounds, while Leonard, *et al.* discloses using anti-IL-12 antibodies. The bis-compounds of Gillies, *et al.* are very different than the anti-IL-12 antibodies of Leonard, *et al.* The bis-compounds are small organic molecules. For example, a typical bis-compound, such as compound 54064 (page 26), has a molecular weight of about 260. In contrast, the anti-IL-12 antibodies of Leonard, *et al.* are heat-labile proteins comprising two light polypeptide chains and two heavy polypeptide chains. The antibodies are large glycoproteins with molecular weights of about 150,000. The bis-compounds are produced by chemical synthesis, while the anti-IL-12 antibodies are expressed by hybridomas. The bis-compounds and the anti-IL-12 antibodies have very different physical, chemical and biological properties. Due to the vast differences of the bis-compounds of Gillies, *et al.* and the anti-IL-12 antibodies of Leonard, *et al.*, there is no reasonable expectation that any successful treatment using one can be duplicated using the other.

Therefore, Gillies, *et al.* in view of Leonard, *et al.* do not render Claims 25, 34-37, and 39-42 obvious. According, Applicants respectfully request the Examiner to withdraw this rejection.

The Examiner rejects Claim 38 as allegedly being unpatentable over Gillies, *et al.* (WO 96/40093) in view of Leonard, *et al.* (U.S. Patent No. 6,338,848) and Gately, *et al.* (U.S. Patent No. 6,225,117).

For the reasons stated earlier, Gillies, *et al.* in view of Leonard, *et al.* do not render Claim 37 obvious. Claim 38 depends from Claim 37. Since Gillies, *et al.* in view of Leonard, *et al.* do not render Claim 25 obvious, Gillies, *et al.* in view of Leonard, *et al.* do not render Claim 38 obvious. Gately, *et al.* does not cure the deficiency of Gillies, *et al.* and Leonard, *et al.*

Gately, *et al.* disclose p75 heterodimer specific IL-12 antibodies for use in blocking IL-12 bioactivity to treat conditions mediated by undesirable IL-12 stimulated immunological responses (col. 2, lines 36-39). Gately, *et al.* disclose the following modes of administration:

> "The IL-12 antibodies may be administered parenterally by injection or by gradual perfusion over time. They can be administered intravenously, intramuscularly, or subcutaneously." (col. 9, lines 33-36).

Gately, *et al.*, similar to Leonard, *et al.*, do not teach or suggest administering the antibodies topically. Similarly, there is no suggestion or motivation to combine Gately, *et al.* with Gillies, *et al.* Further, due to the vast differences between the antibodies of Gately, *et al.* and the bis-compounds of Gillies, *et al.*, there is no reasonable expectation that the treatment of Gillies, *et al.* would successfully treat psoriasis using the antibodies of either Leonard, *et al.* or Gately, *et al.*

Therefore, Gillies, *et al.* in view of Leonard, *et al.* and Gately, *et* al. do not render Claim 38 obvious. According, Applicants respectfully request the Examiner to withdraw this rejection.

The Examiner rejects Claims 25, 35, 37, and 38 as allegedly being unpatentable over Strober, *et al.* (WO 98/16248) in view of Gately, *et al.* (U.S. Patent No. 6,225,117).

The Examiner asserts that: "The ordinary artisan at the time the invention was made would therefore found it obvious to utilize the antibodies of Gately et al. in the

method of treating psoriasis in a patient as taught by Strober et al." (page 8, lines 18-19).

For the reasons stated earlier, Strober, *et al.* neither teach nor suggest the treatment of psoriasis by administering anti-IL-12 antibody alone. Therefore, using the antibodies of Gately, *et al.* in the method of Strober, *et al.*, as suggested by the Examiner, does not cure the deficiency of Strober, *et al.* There is no expectation of success that the using the antibodies of Gately, *et a*l. in the oral tolerance method of Strober, *et al.* (administering IL-12 and anti-IL-12 antibody) would suggest or motivate the claimed method of Claim 25 (consisting the step of administering to a patient a pharmaceutical formulation comprising an antibody that binds to interleukin 12). Claims 35, 37, and 38 depend from Claim 25. Since Strober, *et al.* in view of Gately, *et al.* do render Claim 25 obvious, they also do not render Claims 35, 37, and 38 obvious.

According, Applicants respectfully request the Examiner to withdraw this rejection.

5. Double patenting rejection

The Examiner provisionally rejects Claims 25, 34-37, and 42 under the judicially created doctrine of obvious-type double patenting over Claims 25-26, and 29-32 of copending application ser. no. 10/108,191.

Upon notification of otherwise allowable claims, Applicants intend to file a terminal disclaimer in order to overcome this provisional rejection.

The Examiner provisionally rejects Claims 39-41 under the judicially created doctrine of obvious-type double patenting over Claims 25-26, and 29-32 of copending application ser. no. 10/108,191 in view of Leonard, *et al.*

Upon notification of otherwise allowable claims, Applicants intend to file a terminal disclaimer in order to overcome this provisional rejection.

The Examiner provisionally rejects Claim 38 under the judicially created doctrine of obvious-type double patenting over Claims 25-26, and 29-32 of copending application ser. no. 10/108,191 in view of Gately, *et al.*

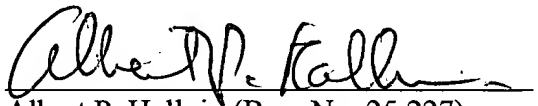
Upon notification of otherwise allowable claims, Applicants intend to file a terminal disclaimer in order to overcome this provisional rejection.

CONCLUSION

In view of the foregoing amendment and remarks, the Applicants believe that the application is in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 463-8109.

Respectfully submitted,

Dated: February 17, 2004



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1: J Dermatol. 1999 Apr;26(4):210-5.

The SAPASI is valid and responsive to psoriasis disease severity changes in a multi-center clinical trial.

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We developed a structured Psoriasis Area Severity Index (PASI)-like instrument, the Self-administered PASI (SAPASI), that allows subjects to assess accurately the severity of their psoriasis. The major limitation of our previous SAPASI validity studies is that all were performed in a single academic center, raising questions about the generalizability of the instrument. We administered the SAPASI to 182 subjects in a 12-week, multicenter, double-blind clinical trial of topical tazarotene for psoriasis. On the same day, investigators blind to the SAPASI rating determined the degree of erythema, induration, scale, body surface area (BSA) affected, and overall lesion severity of the subjects' psoriasis. Using these data, we calculated an investigator PASI-Equivalent. Correlation analysis shows that for both initial and final assessments of psoriasis severity, the SAPASI score reflects the PASI-Equivalent score in a significant way ($p = .0001$), although the correlation is a modest one ($r = 0.3$ to 0.5). Significant ($p = .0001$), modest correlations were found between the subjects' reported BSAs and the investigators' reported BSAs. To assess responsiveness, the proportional changes of the SAPASI and PASI-Equivalent were found to be modestly significantly correlated ($r = 0.2$, $p = .04$). The results of this study support the general validity of the SAPASI and demonstrate that the SAPASI can detect changes in disease severity in a clinical trial. Significant correlations were also observed between SAPASI components and their investigator-reported counterparts in this multicenter trial. To the best of our knowledge, the current study represents the first multicenter validity study performed on a psoriasis severity instrument, and clearly demonstrates the value of this instrument in assessing the psoriasis severity in a population.

Publication Types:
- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

1: Allergy. 1997 Nov;52(11):1087-94.

Monitoring of serologic immune parameters in inflammatory skin diseases.

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This paper deals with the correlation of clinical scoring and serologic marker of inflammation in atopic dermatitis and psoriasis. Serum eosinophil cationic protein (ECP), soluble interleukin-2 receptor (sIL-2R), total serum IgE, IgG and IgM anti-IgE antibodies, and IgE immune complexes were evaluated in monitoring inflammatory skin diseases such as atopic dermatitis and psoriasis. Well-established clinical activity scores were used as standards in recording skin improvement under treatment in a clinical setting. Serum ECP was found to be increased in both atopic dermatitis and psoriasis patients compared to normal controls; sIL-2R and IgE immune complexes were increased only in atopics with increased serum IgE. Anti-IgE antibodies did not show any deviation in both groups of patients. There was a significant elevation of sIL-2R and IgE immune complexes and a nonsignificant elevation of ECP in high-IgE atopics in comparison to those with normal serum IgE. In both groups of patients, there was a significant reduction of ECP and sIL-2R accompanying the improving skin condition. Serum IgE and the other immune parameters failed to respond. In contrast to other studies, serum ECP failed to correspond significantly with disease activity in our study. Our results showed measurable changes of ECP and sIL-2R for atopic dermatitis and/or psoriasis under treatment, but comparison to clinical scores remains difficult due to the different basis of the two systems. The only significant correlation was established for relative changes in sIL-2R and psoriasis area and intensity (PASI), a correlation which might be a useful approach in psoriasis.

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